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The Foamy Viruses

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INTRODUCTION

Foamy viruses possess an ribonucleic acid (RNA)-dependent deoxyribonucleic acid (DNA) polymerase, are present in a wide variety of animals including man, and induce persistent infections in their natural host. These characteristics have stimulated renewed interest in this virus group. Limited reviews of foamy viruses are published as small sections in reviews dealing with viruses of primates and cats (30, 36, 39). This review concentrates on simian foamy viruses (SFVs), but incorporates the limited literature pertaining to other foamy viruses.

Foamy virus infections are characterized by persistence. In 1957, Andrewes summarized the existing evidence suggesting that viruses may exist in the body in a suppressed state, able to infect and perhaps destroy a small group of cells, but unable to establish or re-establish a general or wide-spread infection (2). In persistent viral infections a state of equilibrium is established between the virus and host. The disease expression may be blocked in numerous ways, including active specific immunity of the host, genetic or species resistance to infection, interference by another virus, or defective interfering particles. During the course of infection, the virus may become masked. Shope (1950) defined a masked virus as a virus not directly demonstrable as an infectious agent but its presence is revealed by indirect tests and circumstantial evidence (70). Among the postulated causes of virus masking are: virus bound to antibody, virus present in amounts too small to be detected by techniques used, virus present only in incomplete or noninfectious form, virus in vegetative phase, and incorporation of virus into the genetic material of the host (provirus).

The question of latency and masking in viral infections has taken on special significance during the past 15 years coincident with the extensive use of tissue and cell cultures particularly in preparation of viral vaccines intended for use in man. Cell cultures, organ cultures, explant cultures of tissue fragments and trypsinized tissues, have provided in vitro substrates for virus unmasking and isolation of a plethora of newly recognized viruses. The first demonstration of the usefulness of these techniques was in the isolation of adenoviruses in cultures of human adenoid tissue by Rowe et al. (61); subsequently, numerous viruses were isolated from both normal and diseased tissues. SFV were among the viruses isolated (34, 35, 41, 42, 60, 64, 72) as contaminates in primary cell cultures (20) used to prepare stock virus pools for research and in large scale production of viral vaccines. Numerous lots of kidney cell cultures, if held long enough, would develop "spontaneous" foamy degeneration, which later was shown to be caused by viruses. More recently, a

similar foamy degeneration has been observed in cell cultures from cows, cats, hamsters, and possibly man, indicating widespread distribution of foamy viruses in mammalian species.

A number of viruses induce syncytium formation in cell cultures. The foamy virus group of syncytium-forming viruses considered here are RNA viruses which have a reverse transcriptase and are all morphologically similar (Table 1).

HISTORY

The first reported description of the cytopathic effect (CPE) in spontaneously degenerating cultures of monkey kidney tissue was published by Enders and Peebles in 1954 (20). Although the CPE was similar to the cytopathology caused by measles virus, the absence of inclusion bodies, and the failure of culture fluids to fix complement with measles immune sera indicated that the CPE was not induced by measles virus. Subsequently, Rustigian and coworkers, independently described the isolation of an agent in cultures of *Macaca mulatta* kidney cells which was designated SFV type 1 (64). A second serotype, SFV type 2, was isolated from *M. fascicularis* (41). A third serotype was isolated from *Cercopitheus aethiops* kidney cultures (72). Serotypes 4 and 5 were isolated from Saimiri and Galago monkeys, respectively (44). SFV types 6 and 7 were isolated from numerous chimpanzee tissues (28, 35, 60). Recently, an eighth serotype was isolated from Ateles species (34).

Bovine syncytial virus (BSV) was isolated from both normal cattle and from cattle with lymphosarcomatosis (50). Feline syncytium-forming virus has been isolated from cats with urolithiasis (22), feline infectious peritonitis (29, 75, 78), respiratory infections (29), neoplasms (32, 47, 51, 59), ataxia (15), and without clinical disease (15). A hamster foamy virus was isolated from hamster tissues by Fabisch et al. (24). A virus resembling the foamy viruses was observed by electron microscopy (EM) in tissues from a patient with nasopharyngeal carcinoma (1). Recently, this isolate has been propagated in cell cultures in vitro and has properties similar to the known foamy viruses (21). A virus, serologically related to SFV type 1, has been isolated from peripheral blood cells from a patient with leukemia (77).

TABLE 1. *Foamy viruses*

Simian foamy viruses (9 serotypes)
Bovine syncytial virus
Feline syncytial virus
Hamster foamy virus
Human foamy virus (Echino)

CLASSIFICATION AND NOMENCLATURE

Agreement on classification of foamy viruses is not achieved. Viruses which induce syncytial formation in cell cultures, and which have an RNA genome, contain an RNA-dependent DNA polymerase and morphologically resemble the leukoviruses are assigned to this group. These have been isolated from primates, cows, cats, hamsters, and man and are usually identified by host of origin. The primate and hamster viruses have been referred to as SFV and the hamster foamy viruses, respectively. However, viruses isolated from cows, cats, and man which possess properties similar to the simian and hamster foamy viruses have been referred to as BSV, feline, and human syncytial viruses, respectively. The human syncytial virus has also been referred to as Echino viruses because it possesses long spikes (21).

Viruses which induce syncytia but are not included as members of the foamy virus group are well known and include such viruses as respiratory syncytial virus and measles virus. Although the induction of a foamy appearance in cell cultures is not the most distinguishing characteristic of this group of viruses, we feel that it would be less confusing to maintain the nomenclature of foamy viruses. Andrewes and Pereira (3) have referred to these viruses as foamy viruses and have classified them as "possible" leukoviruses. Fenner et al. (26) have also referred to this group of viruses as the foamy viruses and have included them in the leukovirus group. We believe that the foamy viruses from monkeys, apes, cows, cats, hamsters, and possibly man, should be incorporated as an independent group of viruses or as a subgroup of the leukoviruses (Table 2).

PROPERTIES OF VIRUSES

Isolations and serological relationships. Foamy viruses isolated from various primate

TABLE 2. *Leukoviruses*

C-type viruses
(leukosis-leukemia-sarcoma viruses)
B-type viruses
(mammary tumor viruses)
Mason Pfizer monkey virus
Visna-Progressive pneumonia viruses
Foamy viruses
(primate, cat, cattle, hamster and possible human origin)

species are presented in Table 3. SFV type 1 has been isolated from both *Macaca* and *Cercopithecus* genera including rhesus (*M. mulatta*), cynomolgus (*M. fascicularis*), Formosan Rock Macaque (*M. cyclopsis*), pigtailed Macaque (*M. nemestrina*), vervet (*C. pygerythrus*), and grivet (*C. aethiops*) (6, 23, 36, 37, 39, 41, 48, 49, 55, 62, 64, 66, 74, 76). SFV type 2 has been isolated from both *Macaca* and *Cercopithecus* genera including rhesus, cynomolgus, Formosan Rock Macaque, and grivet monkeys (41, 54, 71, 72). In addition, SFV type 3 has been isolated from rhesus, grivet, and baboon monkeys (71, 72). Foamy virus type 4 was isolated from squirrel (*Saimiri*) monkeys (42), type 5 from African bushbaby (42), types 6 and 7 from chimpanzees (Pan) (28, 35, 60), and type 8 from the spider monkey (*Ateles*) (34). Recently we have isolated a syncytium-forming virus from capuchin monkeys. This virus is not neutralized by antisera prepared against any of the eight known foamy virus serotypes. As shown, the eight serotypes are most conveniently classified into four major groups of non-human primates, the prosimian, Old World primate, New World primate, and the ape family. Because of the reported relationship between serotype 6 and the human foamy isolate, it is likely that the later virus will fall into the group with serotypes 6 and 7 (21).

Foamy viruses of simian, bovine, and feline origin do not serologically cross-react by neutralization (21, 30, 35). Cross-neutralization studies with eight SFVs are presented in Table 4. Serotypes 1 through 6 and 8 are neutralized only by their homologous antisera. SFV type 7 has a low level of cross-reactivity with antisera prepared against SFV type 2, whereas, the type 2 is not neutralized by antisera prepared against serotype 7 virus. Data pertaining to cross neutralization studies with the hamster isolate are not available.

TABLE 3. *Simian foamy virus isolations*

Primate species	Virus serotype isolated
Pro simians	5
Galago	5
Old World primates	1, 2, 3
Rhesus (*Macaca mulatta*)	1, 2, 3
Cynomolgus (*M. fascicularis*)	1, 2
Formosan Rock Macaque (*M. cyclopsis*)	1, 2
Bonnet (*M. radiata*)	Not identified
Pigtailed Macaque (*M. nemestrina*)	1
Vervet (*Cercopithecus pygerythrus*)	1
Grivet (*C. aethiops*)	1, 2, 3
Mangabey (*Cercocebus* sp.)	2
Baboon (*Papio* sp.)	3
New World primates	4,8
Squirrel (*Saimiri*)	4
Spider (*Ateles*)	8
Capuchin (*Cebus*)	Not identified (new type)
Apes	6, 7
Chimpanzee (*Pan*)	6, 7

Existence of common foamy virus group antigens is not satisfactorily demonstrated. Complement fixation (CF) testing of a large number of both rhesus and grivet monkey sera, indirectly indicated the existence of at least two CF antigenic groups (71). Stiles indicated that SFV type 1 should comprise one group and types 2 and 3 comprise a second CF group. Recently, cross reactivity between types 6 and 7 by CF tests (P. Brown, NINCDS, NIH, unpublished data) was demonstrated. To clearly delineate the existence of CF antigenic groups, a thorough cross-checking of all foamy viruses against immune sera specific for each of the foamy virus serotypes is needed.

Morphology. The foamy viruses are spherical viruses which differ slightly in their size and surface projections. These viruses closely resemble the oncogenic RNA viruses (8, 9, 10, 13).

Intracellular particles are ring-shaped, measure 35 to 50 nm in diameter, and consist of an electron opaque shell and an inner electron-lucent center. These particles are usually closely associated with either the plasma membrane or cytoplasmic vacuoles. Extracellular particles and particles within cytoplasmic vacu-

TABLE 4. *Neutralizing antibody to the eight simian foamy viruses*[a]

Simian foamy virus type	Antisera prepared against simian foamy virus types							
	1	2	3	4	5	6	7	8
1	640	0	0	0	0	0	0	0
2	0	160	0	0	0	0	0	0
3	0	0	20	0	0	0	0	0
4	0	0	0	640	0	0	0	0
5	0	0	0	0	640	0	0	0
6	0	0	0	0	0	320	0	0
7	0	10	0	0	0	0	320	0
8	0	0	0	0	0	0	0	20

[a] Neutralization titers are expressed as the dilution of antisera which when incubated with 100 $TCID_{50}$ units of virus, inhibited the development of CPE in HEK cell cultures. The lowest dilution of antisera tested was a 1:10 dilution.

oles (Fig. 1) measure approximately 100 to 140 nm in diameter and consist of an electron-lucent nucleoid and an outer envelope with radiating spikes. The spikes are 5 to 15 nm long, with a tip-to-tip spacing of 5 to 10 nm (Fig. 1) (8–13, 21, 34, 35, 50).

In an early morphological study with the SFV a helical internal component was ob-

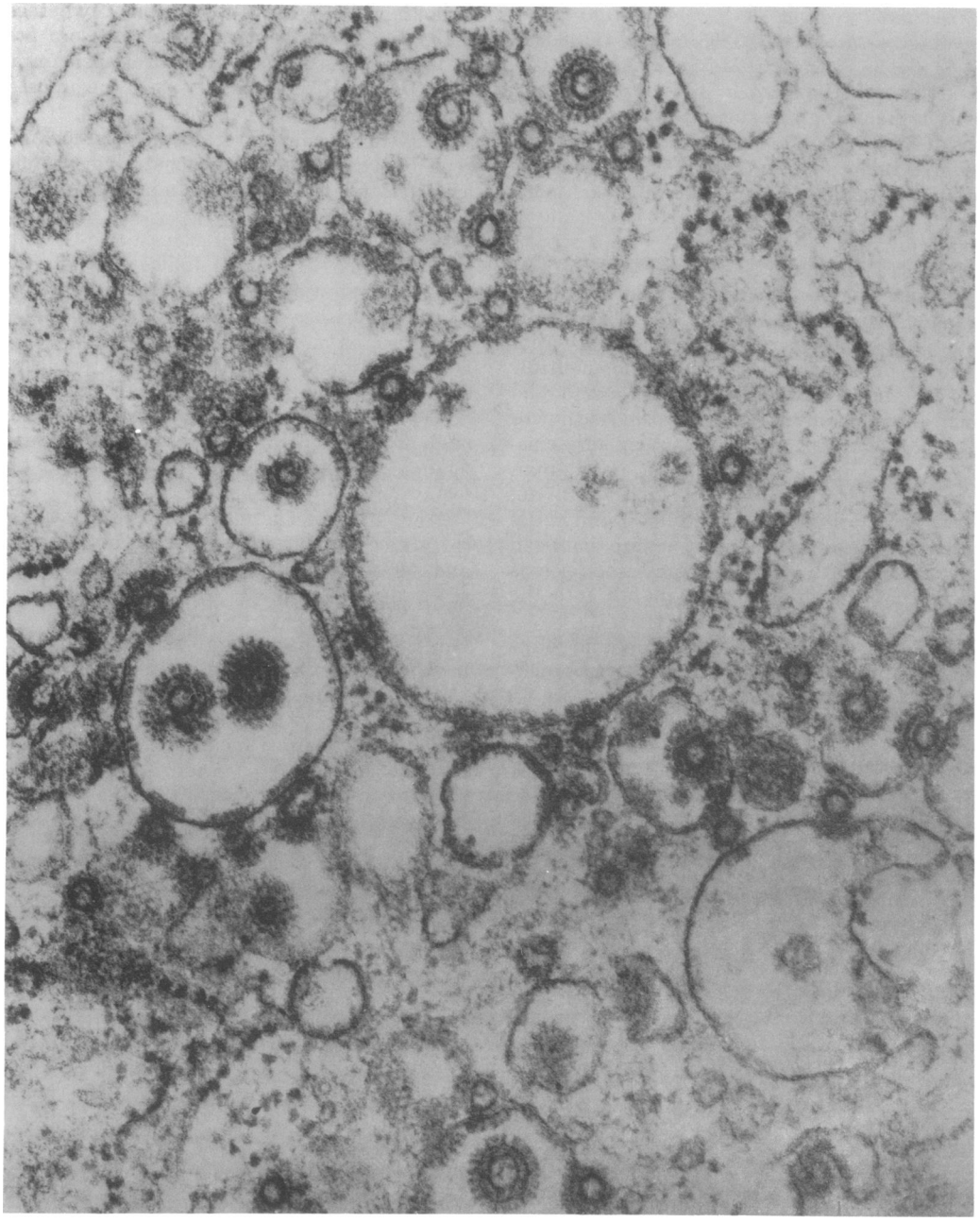

FIG. 1. *SFV type 6-infected HEK cells. Mature virions within cytoplasmic vacuoles. Magnification ×120,000. Cultures were harvested when 75% of the cells in the monolayer developed cytopathic changes as determined by light microscopy. Cells were fixed in phosphate-buffered osmium tetroxide, dehydrated in alcohol, and embedded in Araldite. Ultra-thin sections stained with uranyl acetate and lead citrate were examined with a Siemens electron microscope. (Reproduced with permission from reference 35).*

served, indicating a close relationship between the foamy viruses and the myxoviruses or pseudomyxoviruses (43). Subsequent studies with all of the foamy viruses have not verified the presence of a helical internal component.

Physical and chemical structure. The characteristics of the foamy viruses are summarized in Table 5. Detailed knowledge of the chemical structure of the foamy viruses is not available. Low concentrations of bromodeoxyuridine markedly reduced virus yield (21, 35, 42, 56). In contrast, 5-iododeoxyuridine did not significantly reduce the virus yield. Parks and Todaro have suggested that since the brominated derivative of uridine resembles thymidine more closely than the iodinated derivative, the foamy virus reverse transcriptase may be able to discriminate between the two halogenated thymidine analogues (56).

The SFVs have a buoyant density of approximately 1.16 g/cm^3 in sucrose. SFV types 3 and 8, BSV, and FSV have RNA-dependent DNA polymerase activity with enzymatic properties similar to those of other reverse transcriptase-positive RNA-containing viruses (34, 56, 57, 68). SFV type 3 has been shown to incorporate [^{3}H]uridine and not [^{3}H]thymidine. Treatment of infected cells with actinomycin D inhibits the incorporation of [^{3}H]uridine and decreases the virus yield (56, 57).

Sensitivity to physical and chemical agents. All of the SFV are sensitive to treatment with chloroform and ether (21, 24, 34, 35, 41, 59, 64, 72) and SFV type 7, the only serotype tested, is sensitive to visible light (35). SFV type 3 infectivity is extremely resistant to inactivation by ultraviolet light which is a characteristic shared by the other viruses with a reverse transcriptase (56). The foamy viruses are inactivated after exposure to 56 C for 30 min. In addition, the viruses are still infectious after freezing and thawing and lyophilization. The foamy viruses do not have a detectable hemagglutinin nor has hemaadsorption of guinea pig erythrocytes been observed (21, 24, 34, 35, 41, 42, 59, 64, 72).

Cultivation—host range and cytopathology. The SFVs replicate and induce a CPE in numerous cell lines from a variety of mammalian hosts. The viruses propagate in both epithelial and fibroblastic cells of human, monkey, rabbit, pig, rat, and chicken origin. In addition to inducing cytopathology, SFV type 1 has been reported to induce a carrier state in HEp-2 cells and BHK-21 cells (14).

The SFVs induce CPE in human embryo kidney (HEK) cultures characterized by the formation of vacuolated, foamy syncytia without inclusion bodies (Fig. 2). Initially cytopathic changes consist of small areas of multinucleation. The number of nuclei increase until large areas of multinucleation are seen with extensive vacuolation. The vacuolated or foamy effect is usually not observed until late in the

TABLE 5. *Characteristics of foamy viruses*

Characteristic	
Natural host	Monkeys, apes, cows, cats, hamsters (man?)
Host range	
Lab animals	Rabbit
In vitro (tissue culture)	Wide range
CPE	Syncytium formation
Replication affect by iododeoxyuridine	Not significantly inhibited
Bromodeoxyuridine	Inhibited
Actinomycin D	Inhibited
RNA-dependent DNA polymerase	Positive
RNA size	60S (hamster only)
Density	1.16 g/cm^3
Sensitivity to	
chloroform	Sensitive
pH 3.0	Sensitive
Heat (56 C, 30 min)	Sensitive
Ultraviolet light	Relatively resistant
Visible light	Sensitive
Hemagglutination	Negative
Fluorescent staining	Nuclear, cytoplasmic and cell membrane
Electron microscopy:	
Size:	100–140 nm
	Usually seen in cytoplasm
	Internal component in nucleus associated with chromosomes
	No clearly observable symmetry
	Envelope containing a nucleocapsid
	Electron-lucent nucleoid
	Mature by budding
	Surface projections (spikes)
Replication in vitro	
	Requires dividing cells
	Prolonged latent period
Transformation	
	None observed
Tumor production	
	None observed

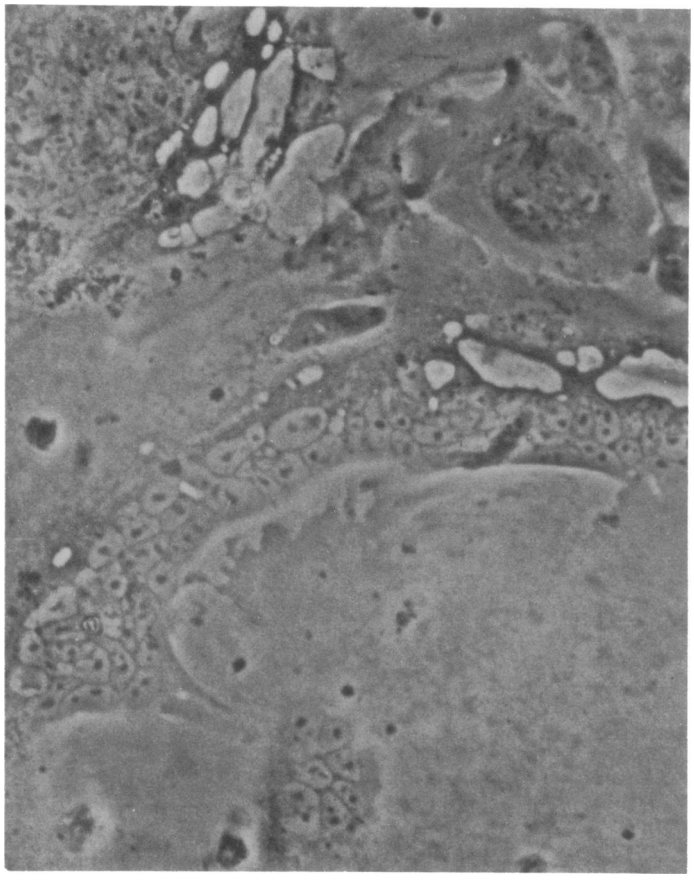

FIG. 2. *CPE induced by SFV type 6 in HEK tissue culture. Magnification ×220. (Reproduced with permission from reference 35).*

infection after a majority of the cells in the monolayer have grossly visible CPE.

The time of the appearance of CPE in vitro varies with serotype of the virus, the virus titer, the passage history, and the type of cells used to propagate the virus. SFV types 1, 2, 3, 6, and 7 generally induce CPE within 4 to 5 days after inoculation of susceptible cell lines and infectivity titers of 10^3 to 10^5 mean tissue culture infective dose ($TCID_{50}$)/ml are readily attainable. SFV types 4, 5, and 8 are more difficult to isolate and maintain than the other foamy viruses. With these serotypes, initial isolation requires holding inoculated cell lines for at least 25 days and in some instances blind passage or subculturing the inoculated cells is necessary. Parks and Todaro (56) have shown that cell multiplication is required for virus replication. For this reason, subculturing of inoculated cells may be required for isolation of these viruses. In fact, this method was used with some early foamy virus infections and was referred to as "unmasking" of the virus (41). Serial rapid passage of all of the SFVs results in a decrease in incubation period and an increase in virus yields.

A typical growth curve obtained with the SFVs is presented in Fig. 3. SFV type 7 was inoculated into HEK cultures at an input multiplicity of 17 $TCID_{50}$ virus doses per cell. Newly synthesized virus which was cell associated was observed only after a latent period of 24 h. The observed CPE and the infectivity titer gradually increased up to day 6, when CPE of 90% was observed and infectivity titer of $10^{5.2}$ $TCID_{50}$/ml for cell-associated sample, and $10^{6.7}$ $TCID_{50}$/ml for supernatant fluid sample was obtained.

Two plaque assay systems have been described for titrating foamy viruses in cell cultures. The first is an agar overlay system described by Parks and Todaro (56). The second is an antibody overlay system. The addition of anti-foamy virus antibody to the maintenance medium will inhibit extracellular spread of the virus. However, the presence of anti-foamy vi-

rus antibody, in a wide range of concentrations, does not inhibit foci of multinucleation which can be read as viral plaques (Hooks, unpublished data).

VIRUS REPLICATION

Attachment and penetration. By EM observations, SFV type 1 has been shown to gain entry into HEp-2 cells either by direct entry or by engulfment of the virion by a cell referred to as viropexis (17, 25). In the direct mode of entry, the virion spikes become attached to the cellular membrane and a break is made both in the cellular and viral membranes. The internal component of the virus subsequently moves deeper into the cytoplasm. Penetration by the direct method occurs most frequently between 0 and 15 min after virus-cell adsorption.

After attachment between the virus and cell membranes, the virus particle may gain entry into the cell by viropexis. During this process the envelope of the virus and the plasma membrane fuse and the virion is carried into the cell within a vacuole. Soon after entry into the cell, the vacuole membrane and the viral envelope are broken down or digested and the viral internal components are released within the cytoplasm. This form of penetration was observed later in the adsorption period (5 min to 60 min).

Multiplication. By fluorescent microscopy (FA) specific foamy virus antigens are detected within the nucleus and cytoplasm and on the plasma membrane of virus-infected cells. The time of appearance of SFV type 1 antigens was studied in HEp-2 cells (27), type 3 antigens in normal rat kidney cells (56), and types 1 and 7 antigens in rabbit kidney cells (Hooks, unpublished data). Although the exact time of events varied slightly in each of these studies, a consistent sequence of events was observed. Viral antigens were initially observed in the nuclei of infected cells approximately 20 h after inoculation. Within a few hours after nuclear staining was observed, cytoplasmic fluorescence was noted around the nucleus. As the infection progressed, nuclear fluorescence was diminished and cytoplasmic staining became more granular. SFV type 1- and 7-infected rabbit kidney cells displayed a membrane fluorescence which was maximal at 24 to 48 h after infection. The distribution of the membrane antigen was patchy and widely dispersed. Nuclear fluorescence has been noted with the other SFVs and with the BSVs, feline syncytial viruses (FSVs), and hamster foamy viruses (7, 27, 35, 50, 56). This nuclear fluorescence is a general characteristic of the foamy viruses which differentiates this group from the oncogenic RNA viruses.

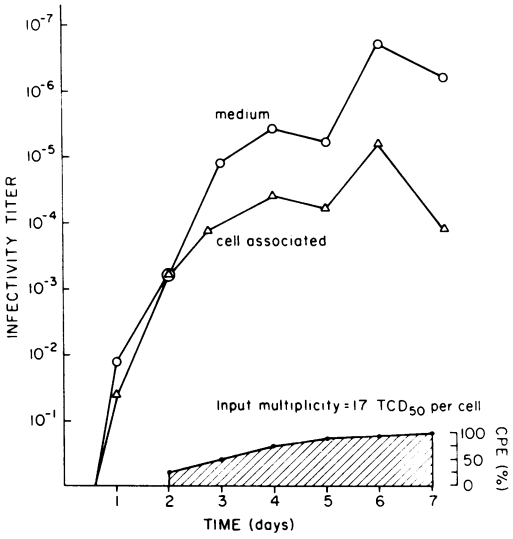

FIG. 3. *SFV type 7 growth curve in HEK cells. Cells were infected at an input multiplicity of 17 $TCID_{50}$ virus doses per cell. After a 90-min adsorption, the inocula was removed and the cells were washed three times. At 24-h intervals, the supernatant fluid and the cells were removed separately and assayed for infectious virus. (Reproduced with permission from reference 35).*

Recently, Dermott and Samuels have demonstrated intranuclear virus particles by EM in cells infected with either BSV or SFV type 1 (18). A virus internal component is located within the structure of the chromosome. This viral internal component present in the nucleus of BSV-infected cells was observed at a time when the virion was replicating. The virus precursor appears to be formed in the nucleus and in some cells is liberated into the cytoplasm by breakdown of the nuclear membrane. In this study, the viral internal components were also observed embedded in the chromosomes of dividing cells.

A viral internal component was also seen located within the structure of the chromosome in HEp-2 cells infected with SFV type 1 (18). It was detected 18 to 24 h after inoculation and before antigen could be detected by FA in this study. Thus, the internal component appeared to originate from the inoculum and had penetrated the cell and had not yet been uncoated. The evidence presented by FA and EM strongly indicate that the foamy viruses enter cell nucleus, become associated with the chromosomes of the cell, and that early replication takes place within the nucleus. The early virus components subsequently enter the cytoplasm by destruction of the nuclear membrane or by a more subtle process.

Once within the cytoplasm, the virus particles mature. Clarke and co-workers (11, 12) have studied the morphogenesis of SFVs in HEp-2 cells and in monkey kidney cells. In the HEp-2 cells, viral internal components which are closely associated with granular material are observed within the cytoplasm. The granular material appears to condense into either internal components or into an array of tubules (diameter 175 ± 2.5 nm). The nature of the tubules is unknown. In the monkey kidney cells, the internal components were associated with extensive areas of endoplasmic reticulum. The endoplasmic reticulum tended to lose ribosomes and become dilated to form vacuoles.

We have also noted tubule-like structures HEK cells infected with SFV type 7 (35). The mode of maturation for most of the foamy viruses consists of budding from the cellular membrane. When the viral internal component is adjacent to the plasma membrane or the cytoplasmic vacuole membrane, the membrane evaginates, spikes are seen on the membrane and the membrane now becomes part of the viral envelope (Fig. 4 and 5).

SFV type 8 appears to mature like the endoplasmic reticulum-associated particles of BSV (4, 34). With SFV type 8, two morphologically distinct viruses are enclosed either by single or double envelopes. The single membrane-envel-

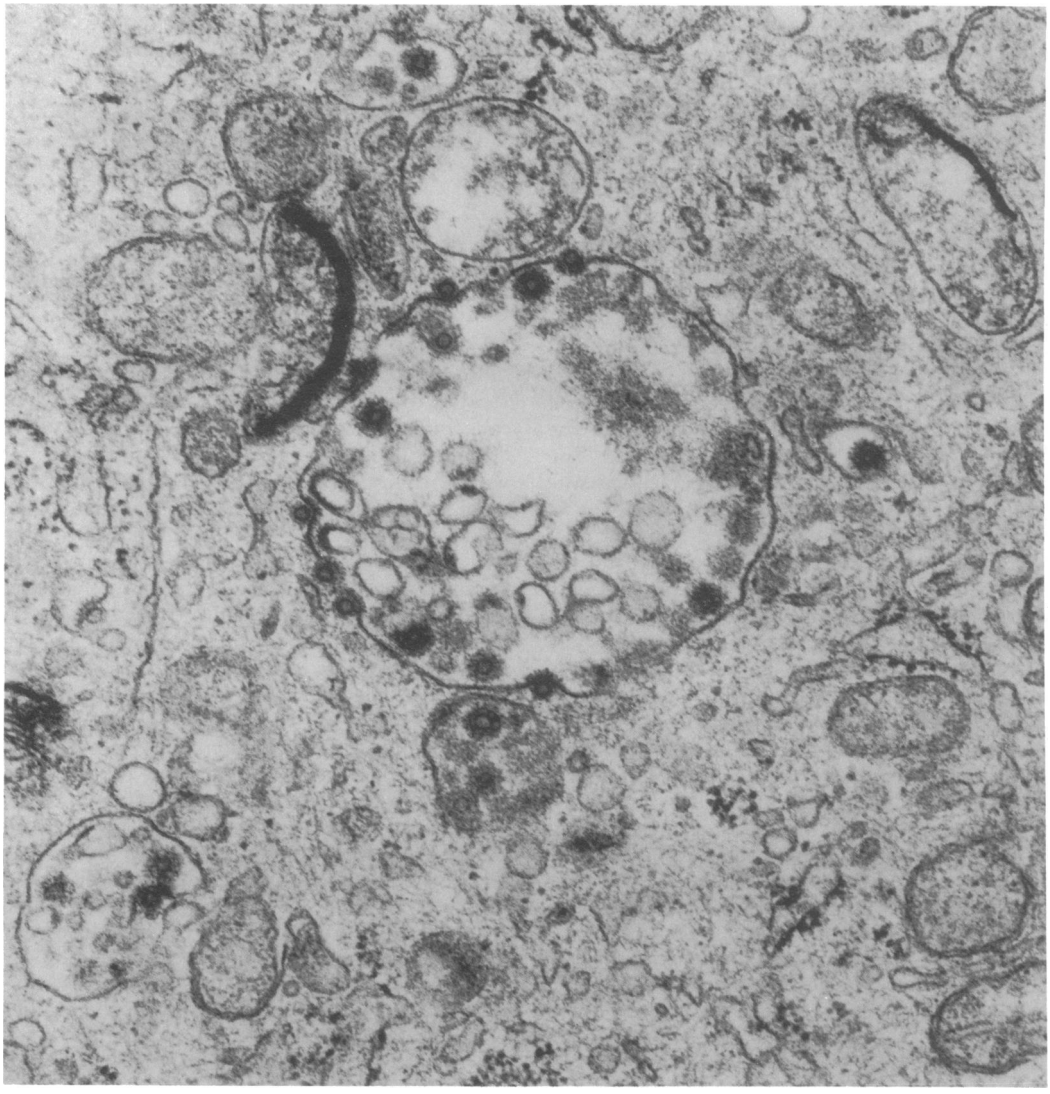

FIG. 4. *SFV type 6-infected HEK cells. Virus particles budding into cellular vacuoles. Magnification ×90,000. Cultures were prepared as described in Fig. 1. (Reproduced with permission from reference 35).*

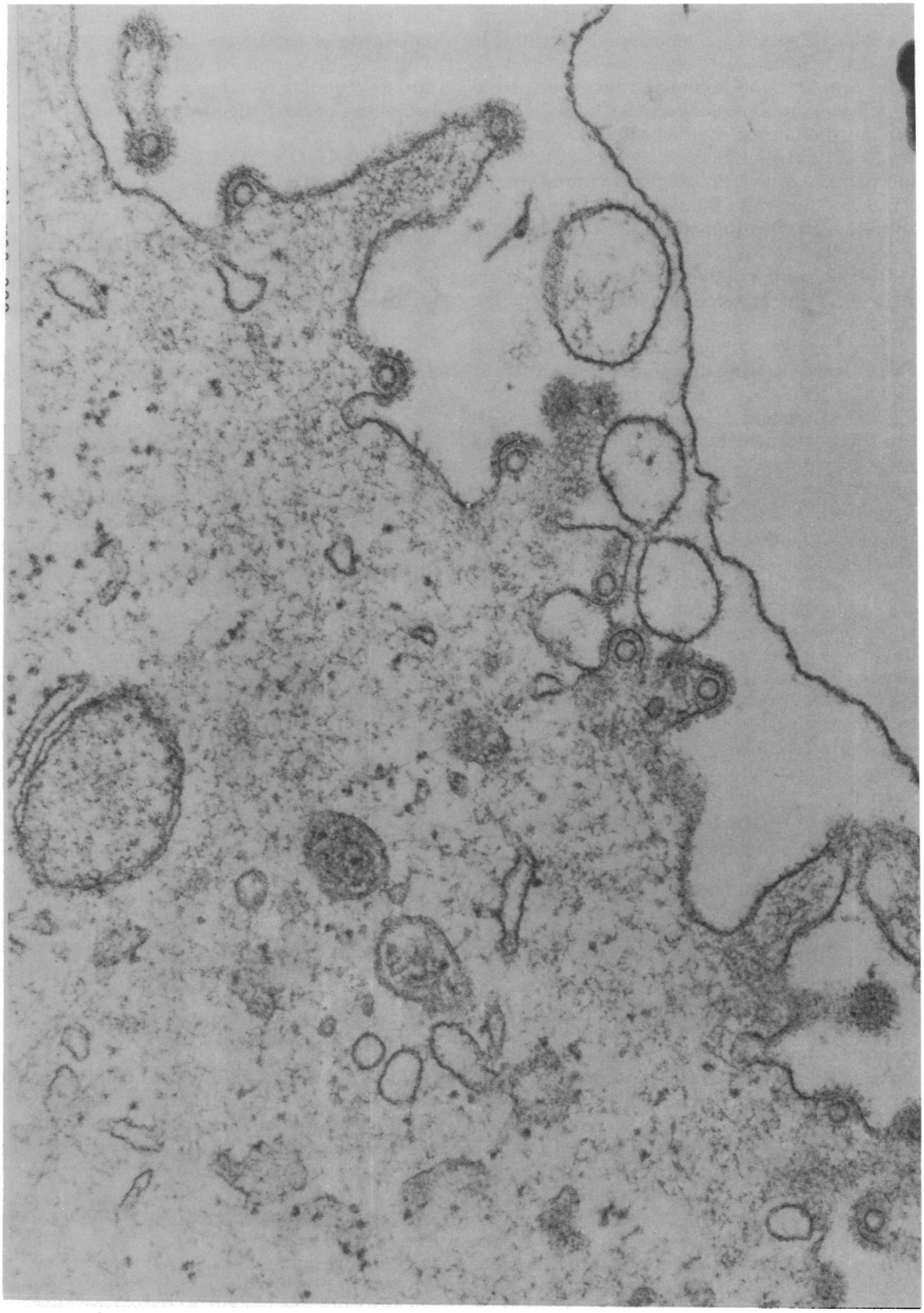

FIG. 5. *SFV type 6-infected HEK cells. Virus particles budding from the plasma membrane. Magnification ×90,000. Cultures were prepared as described in Fig. 1. (Reproduced wi th permission from reference 35).*

oped virions are collected within cytoplasmic vacuoles of smooth endoplasmic reticulum. In contrast, the double membrane-enveloped virions appear to be produced when the tubular membrane profiles enclose the nucleoid. The tubular membrane profiles engulf two or three nucleoids and seem to finally enclose an individual particle to form a complete virion (Fig. 6). Virus budding from the plasma membrane and spikes on the viral envelope have not been observed (34).

Release and viral spread. The virions are released from the cell by budding from the plasma membranes or by destruction of cell and release of virions enclosed in cytoplasmic vacuoles. Viruses are capable of spreading by three different routes or a combination of these routes (53). First, virions released from infected cells can travel by the extracellular route and infect nearby or distant cells. Second, the virus can spread from infected cell to contiguous uninfected cell. Third, viruses or viral genome can be passed to daughter cells during cell division. The first type of spread is exemplified by the enteroviruses and influenza virus; the second type by herpesviruses, and the third type by the leukoviruses. The foamy viruses appear to have the capability to spread by all three routes. The foamy virus plaque formation occurs in the presence of antibody indicating that these viruses can spread by the cell to cell route (Hooks, unpublished data). Since the foamy viruses contain an RNA-dependent DNA polymerase, they have the potential for the third type of spread. An outline of foamy virus replication is presented in Table 6.

Summary. In summary, the foamy viruses initially attach to the cellular membrane by means of the spikes which project from the virus membrane. Penetration takes place either by direct entry or by viropexis. The uncoating process is partially completed with the penetration process and is completed within the cytoplasm or the nucleus. Early steps in multiplication appear to take place within the nucleus since early antigen is detected first in the nucleus by fluorescent antibody studies and the viral internal component is observed within the structure of the chromosome by EM. Since the virions have an RNA-dependent DNA polymerase, viral replication could take place where the viral internal component is observed within the structure of the chromosome. The later stages of multiplication take place within the cytoplasm. Usually viral nucleocapsids are seen budding into cytoplasmic vacuoles or at the cell membrane. At the point of contact between the virus and the cell membrane, the latter becomes thicker and develops spikes, evaginates, and becomes part of the viral envelope. A second mode of development has been observed with the BSV and SFV type 8. With these viruses, tubular membrane profiles within the cytoplasm enclose the viral nucleoids.

RELATION TO LEUKOVIRUSES

The foamy viruses from monkeys, apes, cows, cats, hamsters, and possibly man should be incorporated as an independent group of viruses or as a subgroup of the leukoviruses (26). These foamy viruses most closely resemble the RNA tumor viruses. A comparison of the properties of these viruses is presented in Table 7.

The basic similarities between the two groups consist of a buoyant density of 1.16 g/cm^3, incorporation of radioactive uridine, and not thymidine, inhibition of this incorporation by actinomycin D, sensitivity to bromodeoxyuridine treatment, presence of RNA-dependent DNA polymerase, single-stranded RNA of 60–70S size (hamster foamy), relative resistance to ultraviolet light, and the morphological similarities seen by EM including size, no clearly observable symmetry, and spherical internal component.

There are several major differences between the two groups of viruses: specific intranuclear staining is observed in cells infected with the foamy viruses. The foamy viruses have not been shown to induce transformation in vitro or tumor production in vivo. Group-specific antigens present in C-type viruses are not found in the foamy viruses. By EM the foamy virus internal component has been observed within the nuclei of infected cells. In addition, there are preformed intracytoplasmic particles in foamy virus-infected cells, differentiating them from the C-type viruses. The foamy viruses have an electron-lucent center rather than a dense nucleoid and contain large surface projections.

VIRUS DISTRIBUTION IN VIVO

Natural and experimental hosts. Although the foamy viruses resemble the oncornaviruses, one of the distinguishing characteristics of the foamy viruses is the fact that they do not induce clinical disease in their natural host or in experimental animals.

The foamy viruses have been isolated from numerous tissues from both normal and clinically ill apes, monkeys, cows, and cats. Usually, the natural host has high levels of circulating antibody against the homologous virus isolated from its tissues. Johnston repeatedly isolated foamy virus from monkey throat swabs over a 10-week interval (41). Thus, these vi-

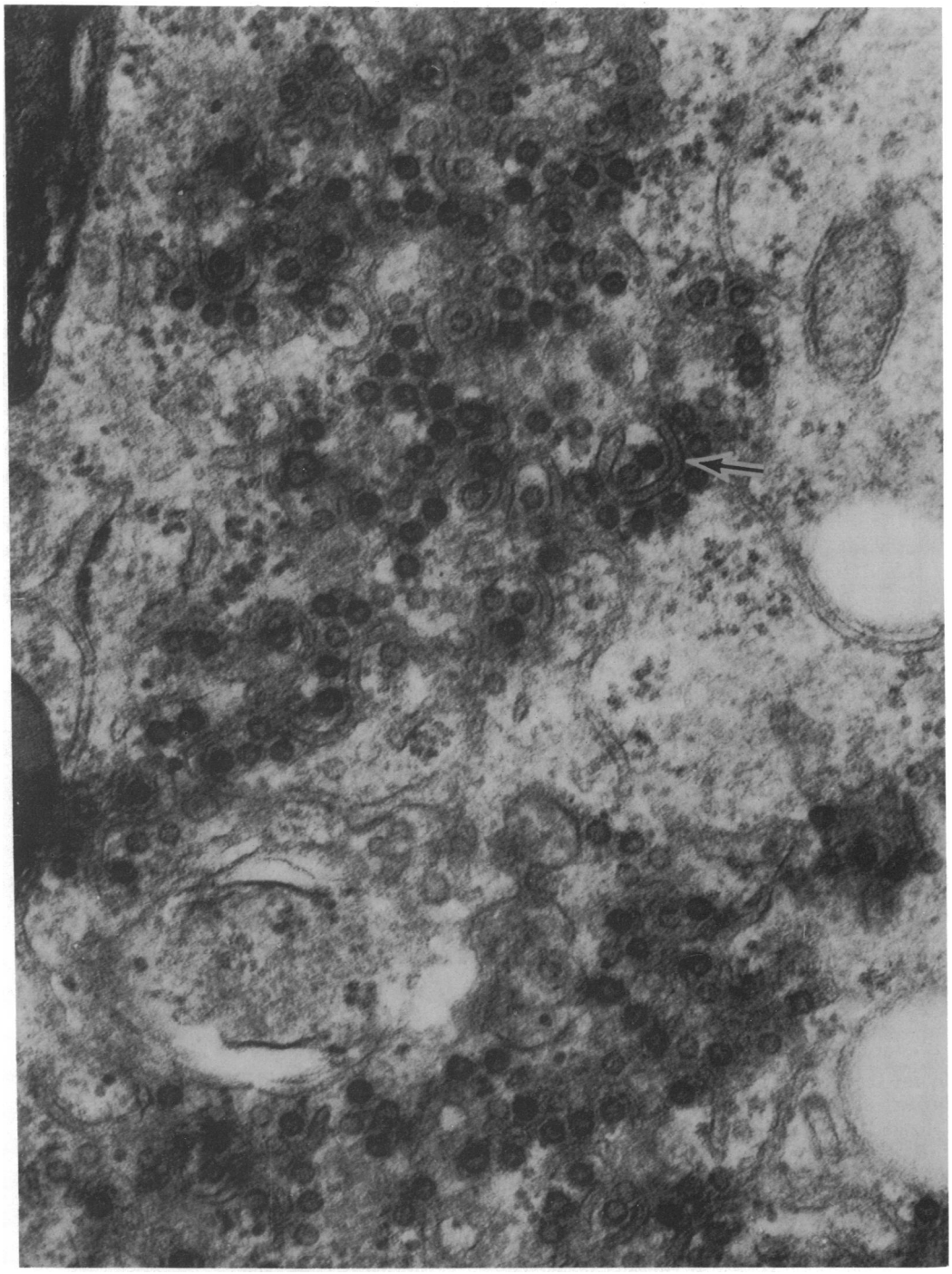

FIG. 6. *SFV type 8-infected HEK cells. Tubular membrane profiles engulfing nucleoids are seen to enclose a particle and form a complete virion. (Arrow) Magnification ×72,000. Cultures were prepared as described in Fig. 1. (Reproduced with permission from reference 34).*

TABLE 6. *Foamy virus replication*

Attachment:
Attaches by means of spikes
Penetration:
Direct entry
Viropexis
Uncoating:
Cytoplasm (may be completed in the nucleus)
Multiplication:
Early: nucleus (based on FA and EM)
Late: cytoplasm
Release:
Budding (into cytoplasmic vacuoles or at the plasma membrane)
Membrane profiles enclose nucleoid

ruses appear to persist in their natural host in the presence of high levels of circulating antibody. Similarly, in our own studies, we have been able to demonstrate the long term persistence of neutralizing antibody in chimpanzees (35). This is consistent with the notion that these viruses persist in their natural host.

Inoculation of the foamy viruses into sero-negative natural hosts results in sero-conversion but no signs of clinical disease (50, 51, 63). In addition, the inoculation of these viruses into laboratory animals such as rabbits, newborn and adult mice and hamsters, guinea pigs, day-old chicks, and embryonating hens' eggs has not resulted in clinical disease (34, 35, 41, 42, 51, 59, 64, 72).

SFV type 1 inoculated into rabbits by the intraperitoneal route persists in the rabbit tissues without inducing clinical disease. One to three weeks after inoculation, the virus could be isolated from several tissues with the highest infectivity titer in the spleen, liver, lungs, and salivary glands. Kidney cell cultures from rabbits with serum-neutralizing antibody yielded virus 74 days after infection (N. S. Swack and G. D. Hsuing. Abstr. Annu. Meet. Am. Soc. Microbiol. 1974, V192, p. 234). Moreover, SFV types 1 and 7 inoculated into rabbits by the intravenous route can be recovered from buffy coat cells 10 days after inoculation (Hooks, unpublished data). It appears as though the persistent infection in the rabbit is similar to the persistent infection found in the natural host.

Mechanism of virus spread. The mechanism of virus spread within a population is not fully understood. However, there is experimental evidence for both horizontal and vertical viral spread. Since the SFVs have been isolated from throat washings and not from urine or feces, it would appear that horizontal transmission could take place by direct contact and by the respiratory route. In fact, monkeys without antibody to the foamy viruses have been shown to develop antibody 1 to 3 months after entry into a primate colony (63). However, horizontal spread does not necessarily have to occur in a primate colony. Eighty-eight percent of our chimpanzees had demonstrable neutralizing antibody to either or both SFV serotypes 6 and 7. Two chimpanzees remained sero-negative for 2 years in our colony (35). Vertical virus transmission has been demonstrated by the isolation of a foamy virus from a pregnant rhesus monkey cervix, placenta, and the kidney of the fetus (Asher and Hooks, unpublished data). The FSVs have been isolated from nasal swabs, pharyngeal swabs, and from urine (30). Again, horizontal transmission probably takes place by the respiratory route. FSV has also been isolated from 15% of cat fetuses tested (32) and from two primary cultures of feline embryonic cells (40).

The distribution of the virus within the host is widespread. For example, we have isolated SFV types 6 and 7 from the following chimpanzee tissues grown in vitro: brain, spinal cord, sympathetic ganglia, spleen, thymus, kidney, lymph node, salivary gland, and lung. We have

TABLE 7. *Comparison of properties of the foamy viruses and the oncornaviruses*

Similarities	Differences
RNA-dependent DNA polymerase	FA: Nuclear and cytoplasmic staining
Sensitive to bromodeoxyuridine treatment	No transformation in vitro
Sensitive to actinomycin D treatment	No tumor production
Density of 1.16 g/cm^3	No group-specific antigen (different from C type)
Single-stranded RNA of 60-70*S* size	EM
Chloroform sensitive	Nuclear internal component
pH sensitive	Electron-lucent nucleoid
Heat (56 C, 30 min) inactivated	Preformed cytoplasmic particle (different from C type)
Ultraviolet treatment—relatively resistant	
Hemagglutination negative	Large spikes
Prolonged latent period	
EM: size 100 nm	
No clearly observable symmetry	
Spherical internal structure	
Envelope containing a nucleocapsid	
Mature by budding	

not been able to isolate the viruses from 10% suspensions of those tissues. Recently, we have isolated SFV type 6 or 7 from buffy coat suspensions of three chimpanzees. However, numerous attempts to isolate foamy viruses from the urine and whole blood from these same chimpanzees were unsuccessful. FSV has been isolated from cell cultures derived from omentum, thymus, lymph node, lung, kidney, and whole embryo (29). In addition, the virus was isolated directly from nasal swabs, pharyngeal swabs, urine, and whole blood (30). BSV has been isolated from buffy coat cells and cellular elements present in milk (50). The presence of virus in the buffy coat could explain the mechanism of viral dispersal within the natural host.

SERO-EPIDEMIOLOGY

The distribution of antibody to the foamy viruses is relatively species specific and widespread within the natural host population. Numerous investigators have shown that there is a high degree of correlation between the presence of circulating antibody, demonstrated either by neutralization, CF or FA and the ability to isolate the viruses (7, 34, 35, 41, 42, 62, 71).

One of the major problems in trying to determine the distribution of the foamy viruses in primates is the fact that many different species are usually housed in close proximity. Studies demonstrating the sero-conversion of monkeys from foamy virus antibody negative to positive upon entry into primate colonies has previously been mentioned. Sera collected from animals at the time of capture has been used in some studies. In addition, valuable data concerning the distribution and spread of these viruses in primates can still be obtained from primates housed in captivity.

The distribution of neutralizing antibody to the foamy viruses in humans and subhuman primates is summarized in Table 8. The species from whom the virus serotype has been isolated has the highest percentage of animals with neutralizing antibody.

Data pertaining to the distribution of foamy virus-neutralizing antibody in sera collected from animals recently captured, is incorporated within Table 8. Ruckle found that 70% of the cynomolgus monkeys that arrived at a holding facility had neutralizing antibody to SFV type 1 (64). Sera from 5 of 24 baboons bled after capture contained neutralizing antibody to SFV type 3 (45). Sera collected from 16 chimpanzees in the African bush contained neutralizing antibody to either or both SFV types 6 and 7 (35).

Distribution of CF antibodies to SFV type 1 in rhesus monkeys and serotype 2 in grivet monkeys were examined over a 4-year period

TABLE 8. *Distribution of neutralizing antibody to the simian foamy viruses*[a]

Serum source	Simian foamy virus type							
	1	2	3	4	5	6	7	8
Human								
Natural habitat	0/100, 0/7	0/100	1/21	0/80	0/80	0/13	0/13	0/1
Laboratory workers	0/8		1/20	0/6	0/6	0/9	0/9	0/16
Pooled serum	0/5, 0/1	0/5						
Primates in captivity								
Gorilla			0/1			0/1	0/1	
Chimpanzee			3/29			67/104	64/101	0/10
Orangutan			5/19					
Baboon		8/21	22/65					
Rhesus	16/29, 7/14, 33/34	8/14, 11/11				3/7	0/7	0/9
Cynomolgus						2/7	2/7	
Vervet			5/18			0/6	0/7	
Squirrel	0/8	0/8	0/8	12/19	0/8	0/6	0/6	
Galago	0/12	0/12	0/12	0/12	5/6			
Spider	0/33	0/22	0/8	0/7	0/2	0/7	1/7	19/31
Primates in natural habitat[b]								
Chimpanzee						12/16	7/16	
Baboon			5/24					
Rhesus	2/22							
Cynomolgus	37/57							

[a] The data presented in this table was obtained from references (34, 35, 41, 42, 46, 63, 64).

[b] The serum source entitled "Primates in natural habitat" refers to sera collected from primates recently captured and sera collected upon arrival of the primate at a primate holding facility.

(72). The percentage of monkeys containing CF antibody were similar to that with neutralizing antibody, that is, 50% of rhesus monkeys had CF antibody to serotype 1 and 60% of grivet monkeys had CF antibody to serotype 2.

The search for antibody to the SFVs in human sera has not been very extensive. Most studies have not demonstrated antibody to the foamy viruses in human sera (Table 8). However, Kalter has reported the presence of neutralizing antibody to SFV type 3 in one of 21 human sera collected in Africa and in one of 20 human sera from a worker at the Southwest Foundation for Research (45). It is important to extend these serological studies in humans for the following reasons: the foamy virus group could have a human counterpart which may contain antigens cross-reacting with the known SFVs. The viruses have a reverse transcriptase and have been seen by EM or isolated in two cases of human cancer. Finally, these viruses may have been in some of the early poliovirus vaccines.

Numerous sources of sera, other than primate sera, have been examined and are not included in the table. None of the following animals have antibodies to the SFVs: rabbit, horse, cow, pig, goat, sheep, dog, chicken, mouse, hamster, or guinea pig.

The presence of FSV also appears to be widespread in cat populations. The incidence of FSV based upon isolation of virus ranged from 30% in one study to 90% in a second study (29, 59). Gaskin has demonstrated a 100% correlation between the presence of precipitating antibody and the presence of virus in 36 cats tested (29). The presence of precipitating antibody to FSV was observed in 50 of 180 cat sera tested (29).

The distribution of precipitating antibody to BSV in bovine sera from normal and diseased cows was investigated by Malmquist et al. (50). Precipitating antibody was detected in 139 of 462 sera tested. The presence of antibodies to the FSVs and BSVs in human populations has not been reported.

VIRAL PERSISTENCE

As we have mentioned previously, the foamy viruses induce a persistent infection in their natural host. There are numerous factors which could play a role in the induction and maintenance of persistent viral infections (Table 9). Non-immunogenicity and non-neutralizing antibody, probably are not instrumental in foamy virus infections (26, 52). Although defective interfering particles, temperature-sensitive mutants and defective cell-mediated immunity may be involved in persistence of foamy virus, there is no evidence suggesting that this is the case (38, 52). In contrast, there is evidence to suggest that integration of genomes, poor induction of interferon, relative insensitivity to antiviral activity of interferon, and mode of viral spread, all may play a role in the persistence of the foamy virus infections (31, 44, 52, 53).

TABLE 9. *Mechanisms of viral persistence*

Mechanism	Possible role in foamy virus persistence
Integration of genomes	Yes
Interferon:	
Poor inducer	Yes
Relative insensitivity	Yes
Mode of viral spread	Yes
Defective interfering particles	Unknown
Temperature-sensitive mutants	Unknown
Defective cell-mediated immunity	Unknown
Non-immunogenicity	No
Non-neutralizing antibody	No

Integration of genomes could be a factor involved in the persistence of foamy virus infections. The RNA tumor viruses appear to be able to persist as DNA copies of their genome integrated into the cellular genome. The presence of an RNA-dependent DNA polymerase in the foamy virus would enable these viruses to persist by this mechanism.

The low capacity of a virus to induce interferon, as well as the relative insensitivity of that virus to the inhibitory activity of interferon, have been related to the persistence of certain viruses in an infected host. For example, cytomegalovirus has been associated with long term chromic infections in humans and displays these characteristics (31). More specifically, interferon induction could not be demonstrated in feline cell cultures infected with FSV (32). Also, we have recently demonstrated that four serotypes of the SFVs are both poor inducers of interferon and are relatively insensitive to the antiviral activity of interferon (Hooks, unpublished data).

The mode of spread of a virus and the relationship between viral spread and the immune response may be important factors in viral persistence. We have stated previously that foamy viruses can spread directly from infected cells to contiguous uninfected cells. Viruses which spread by this route induce virus-specific antigens on the surface of infected cells. Ideally, the addition of antibody and complement to these infected cultures would result in destruction of infected cells and neutralization of extracellular virus.

The foamy viruses induce virus-specific anti-

gens on the plasma membrane of infected cells. However, anti-foamy virus antibody and complement does not destroy these cells (Hooks, unpublished data). Recent studies have demonstrated that the addition of antibody may result in capping of viral antigens on the cell membrane and thus prevent cytotoxicity of these cells when complement is added (44). However, we have not been able to demonstrate capping with foamy virus-infected cultures. The concentration and/or distribution of viral antigens on the cell membrane could be another explanation of the failure of immune lysis. Foamy virus antigens present on infected cell membranes are widely dispersed or patchy, in comparison to the high concentration and close proximity of herpes simplex virus or measles virus antigens on infected cell membranes (Hooks, unpublished data). Thus, the spread of foamy virus from infected cell to contiguous uninfected cell and the absence of antibody-mediated lysis may enhance the chances for foamy viruses to persist.

The above mechanisms of viral persistence acting alone or in conjunction with each other could be operative in foamy virus-persistent infections. Whether or not defective interfering particles, temperature-sensitive mutants or a defective cell-mediated immunity play a role in foamy virus persistence remains to be determined.

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